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Title: Delivery Device for Delivery of a Composition that Reacts to Heat

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The documents attached to this page are a copy of the originally filed description with claim(s) and any drawing(s).

DELIVERY DEVICE FOR DELIVERY OF A COMPOSITION THAT REACTS TO HEAT

The invention concerns a new and useful delivery device. In particular, the invention concerns an osmotic device for delivery of a heat-sensitive composition with a medical agent in it to a surrounding medium at a controlled flow rate.

Delivery devices for delivery of medical agents to a surrounding medium are known in the art. For example, US Patent 3 760 984 (Theeuwes) discloses such a device, consisting of a heat-shrinkable vessel with an osmotic solute on its external surface and a separate layer of polymer material permeable to liquid. The delivery device is provided with a plug for filling of the vessel. This device is activated by the liquid impregnating it by penetrating it and dissolving the solute to form a solution that exerts a pressure against the shrinkable vessel whose contraction delivers the agent. US Patent 3 865 108 (Hartop) discloses a device consisting of a compressible internal tube that contains a drug placed in a base element formed from a swellable material. The device delivers the drug through the base and parts of the surrounding medium are absorbed and press against the compressible tube so that the drug is driven from the tube. In US Patent 3 971 376 Wichterle discloses another device consisting of a capsule with walls formed from a crosslinked gel that swells in liquids. A textile fabric is accommodated in the material to impart strength to it and reduce difficulties due to the poor mechanical characteristics related to the material, which appear during absorption of the liquid used to operate the device. In US Patent 3 987 790 Eckenhoff discloses an improvement made to an osmotic device formed from a line for filling of a sack situated in the device. The device is activated by a solute with osmotic action that impregnates it with liquid, a liquid that produces a hydraulic pressure against the sack, compressing it and causing the agent to escape. US Patent 3 995 631 (Higuchi c.s.) describes a sack carrying on its external surface a layer of osmotic solute with a separate wall formed of a material with controlled permeability relative to liquids. During operation a solution of the solute is formed, which compresses the sack, causing the agent to escape. In US Patent 4 320 758 Eckenhoff discloses a device formed from a flexible sack with a covering made of a dispersion of the solute with osmotic action in a soluble polymer and a liquid-permeable external wall, a device that delivers the drug through the covering by being impregnated with water in the space between the wall and sac, thus exerting a hydraulic pressure on it that causes the drug to be released.

If the devices just described are of useable for delivery of numerous agents to a surrounding medium, and if they represent progress in this art, specialists can see that there are cases in which new improvements would be of greater commercial interest. For example, a device without the flexible sack and without fabric, thus providing an improvement by reducing the number of operations and necessary parts, would find immediate acceptance and represent substantial progress. Moreover, a device that permits elimination of the limits of the prior art, namely, delivery of agents only in the form of solutions or suspensions with a device that now delivers agents that are soluble or insoluble in liquids, semisolid or in other forms would also be appreciated and also represent a valuable contribution to the fields of science, medicine and commerce.

The object of the present invention is therefore to devise a new delivery device for delivery of medical agents in all forms to a surrounding medium that entails an improvement in the metering technique.

Another object of the invention is to devise a self-contained, self-activated and self-operated device in liquid media, easy to manufacture and useable for delivery of agents to animals, including man, as well as other media, biological or not.

Another object of the invention is to devise a delivery device that can contain a heat-sensitive hydrophobic composition that contains insoluble or soluble drugs, a composition which, under the influence of temperature of a biological medium, changes form and becomes liquid or semisolid to accelerate delivery from the device.

Still another object is to devise a delivery device comprising a compartment containing a heat-sensitive composition, a dilatable element partially surrounding this composition, an external semipermeable wall enclosing the element and the compartment, and a delivery passage, a device that delivers the composition by the combined physical-chemical effects of melting and making it liquid or semisolid and maintaining a non-miscible separation limit at the interface of the element that dilates, swelling it and displacing an equivalent amount of the composition from the device.

Still another object of the invention is to devise a delivery device that is empty until it is filled with a solid composition that liquefies when heated and, once filled, can administer this liquified composition according to a complete pharmaceutical dosage regime over a certain period of time and whose use only requires intervention at the beginning and end of the regime.

Another object is to devise a delivery device that can deliver drugs contained in a heat-sensitive lypophilic pharmaceutical vehicle that melts under the influence of heat, producing a composition that can be delivered without difficulty, avoiding irritation of tissues of mammals and interaction with protein tissues of mammals.

Another object is to devise an osmotic delivery device containing a eutectic composition formed from at least two components and one or more drugs, a composition whose melting point is essentially the same as the temperature of a warm-blooded animal and which is delivered to the animal at this temperature.

Another object is to devise a delivery device that can contain a heat-sensitive hydrophilic composition containing insoluble to soluble drugs, a composition, which, under the influence of heat of a biological medium, changes form and can be delivered to the surrounding medium.

Another object is finally to devise a delivery device that contains a chemically unstable agent in a surrounding aqueous medium and can be accommodated in a nonaqueous carrier, an agent that is protected in this vehicle during delivery from the device.

Other objectives, characteristics and advantages of the invention are apparent from the following description, drawings and claims.

BRIEF DESCRIPTION OF THE DRAWINGS

In the drawings, which are not to scale but are given only to illustrate various versions of the invention, the figures have the following meanings:

Figure 1 is a view of a device designed and manufactured for oral administration of drugs to a warm-blooded animal;

Figure 2 is a cross section of the device of Figure 1 along line 2-2 of Figure 1 to show the internal compartment and the thermodynamic elements forming the produced system in an integrated delivery device;

Figure 3 is a cross section of the device of Figure 1 showing the compartment filled with a temperature-sensitive composition that contains the agent being delivered;

Figure 4 is a cross section of the open device of Figure 3 showing dilation of the control elements that deliver the agent from the device;

Figure 5 is a cross section of Figure 1 showing a closure element in the compartment;

Figure 6 shows a variant of the invention in which the elements forming the device are in concentric arrangement;

Figure 7 shows a variant of the invention in which the elements forming the device are in a partially circular arrangement;

Figure 8 shows a variant of the invention in which the elements forming the device are in a parallel arrangement;

Figure 9 shows a variant of the invention in which the elements forming the device are in the form of a pouch;

Figure 10 is a diagram of three methods for production of the delivery device of the invention;

Figure 11 is a graph showing the delivery rate versus time of a delivery device;

Figure 12 is a graph showing the total amount of heat-sensitive composition delivered by the device.

The same parts of the figures in the drawings and description are identified by the same numbers. The terms and variants occurring previously in the description and in the description of the drawings are explained elsewhere in the description.

DETAILED DESCRIPTION OF THE DRAWINGS

The drawings are examples of new and useful delivery devices for delivery of a medical agent and should not be interpreted as limiting.

An example of a delivery device is shown in Figure 1, where it is identified by the number 10, containing a body 11 with a wall 12 and a passage 13 in this wall that connects the exterior to the interior of the device, as is apparent in Figure 2.

Figure 2 is a cross section of Figure 1, showing the device 10 containing body 11, wall 12 surrounding an internal compartment 14 and a passage 13 in this wall that causes compartment 14 to communicate with the exterior of the device. Wall 12 is formed from a semipermeable polymer material forming a composition that is permeable to passage of an external liquid but practically impermeable to passage of an agent and other ingredients contained in compartment 14. This wall 12 is not toxic and it retains its physical and chemical integrity during use of the device.

Compartment 14 is also surrounded by a layer 15 of a dilatable operating element that is in contact with the internal surface of wall 12, this internal layer 15 partially surrounding compartment 14, except for a part 16 defined by the end 17 of layer 15, and the internal layer 15 has a shape corresponding to that of the semipermeable wall 12 and compartment 14. Layer 15 is made from a hydrogel composition, not crosslinked or optionally crosslinked, and it has osmotic properties, can be impregnated with an external liquid through the semipermeable wall 12 and exerts an osmotic pressure gradient through this wall against a liquid external to device 10.

Figure 3 shows the device 10 of Figure 1 in cross section. In Figure 3 the device encloses the structural elements described with reference to Figures 1 and 2 and showing the device containing in compartment 14 an agent 18 represented by points and a heat-sensitive composition 19 that responds to the action of heat, shown by wavy lines, a composition that is a means of delivery and a transport vehicle for agent 18. Agent 18, which is placed in compartment 14 and can be liberated by the device, contains insoluble to very soluble agents in aqueous liquids and in lipophilic media. The heat-sensitive composition 19 containing the agent 18 dispersed homogeneously or heterogeneously or in solution is formed in a now preferred variant from an anhydrous heat-sensitive hydrophilic or hydrophobic material, solid at ordinary temperature of about 20°C and its melting point is close to the temperature of 37°C of a mammal. In the present invention, the terms "melting point", "softening point" or "become liquid" indicate temperatures at which the heat-sensitive composition melts, partially or totally dissolves, forming a vehicle that permits delivery of agent 18 from 19.

When the delivery device 10 is in a medium with a temperature of about 37°C, it releases agent 18 by a combined thermodynamic and kinetic effect. The heat-sensitive composition 19 melts, forming a fluid or semisolid phase that delivers the agent 18 through passage 13. When composition 19 melts, the liquid impregnates the semipermeable wall 12 through the hydrophilic layer 15 with a tendency toward osmotic equilibrium for continuous swelling, or dilates and increases the volume of layer 15, which dilates at the same time in compartment 14, while maintaining a nonmiscible separation limit at the interface. At the same time as layer 15 increases its volume, it applies a pressure against composition 19, reducing its volume. The simultaneity of dilation of layer 15, contraction of compartment 14 and melting of composition 19 makes the fluid composition containing agent 18 pass through passage 13 to reach the exterior of device 10. Figures 3 and 4 taken together show the device 10 in operation, delivering agent 18. Figure 3 shows the device 10 at the beginning of one period of delivery of the agent and Figure 4 shows it near the end of the delivery period. Melting of composition 19 and its non-miscibility are added on the expansion layer 15 to swelling and dilation of this layer, which is accompanied by an increase in volume, as shown in Figure 4, with a corresponding reduction in the volume of compartment 14 at the same time, as also shown in Figure 4, which ensures gradual delivery of agent 18 at a controlled rate.

Figure 5 is a variant of device 10 of Figures 1 to 4, also showing a closure element 20 in the open end of compartment 14. This closure 20 is well adapted in compartment 14 and is in contact with the inside surface of layer 15. The exterior of closure 20 forms a liquid-tight joint with the internal surface part of layer 15 with which it is in contact. Closure 20, also called a plug, contains a central axial opening 21 that extends completely through it, an opening that gives access to the interior of device 10, chiefly compartment 14, to provide it with the composition 19 containing agent 18 and at the same time opening 21 gives access to passage 13 through the semipermeable wall 12 to deliver the composition 19 containing agent 18.

Figures 6 and 7 show other variants of the delivery device 10 according to the invention. The delivery device 10 of Figures 6 and 7 is made in a now preferred manufacturing process by coextrusion of the structural elements of device 10. In Figure 6, device 10 is shown again with its ends 22 and 23 open to show its structure. This device is essentially formed from the semipermeable wall 24 enclosing its entire exterior before the ends 22 and 23 are opened to show the structure of the device, a median swellable and dilatable thrust zone 25 and an internal heat-sensitive zone 26 as reservoir for the agent. The device 10 also comprises two delivery openings 27 in the semipermeable wall 24 for delivery of the formula of the agent from the closed ends 22 and 23 not shown in Figure 6. Figure 7 shows the device 10 comprising a semipermeable wall 28 surrounding and delimiting the interior of the device in cross section on its ends 29 and 30 to show the internal reservoir 31 of the agent and a contact layer of a swellable and dilatable thrust element 32. The device 10 has three delivery openings 33 through the semipermeable wall 28 that communicate with the reservoir of agent 31 to deliver it. One opening is placed in the body of device 10 and the two others are placed on its closed ends. The device 10 of Figures 6 and 7 functions as described above in its surrounding use medium.

Figure 8 shows the delivery device 10 in a rectangular shape; however, it can also have other shapes and dimensions adapted for its use in specific fluid media. The device in Figure 8 is open along its two side edges to show the internal arrangement. It contains a delivery opening 35, a semipermeable wall 36, a compartment 37 with a heat-sensitive composition 38 containing agent 39 and a swellable and dilatable thrust composition 40. This device

operates to liberate agent 39, as mentioned above, i.e., the heat sensitive composition 38 melts at a temperature of 35 to 41°C and the composition 40 is dilated and the composition 39 is forced through opening 35.

Figure 9 shows a delivery device 10 that has different dimensions for use as a metering pump. In this variant the device is miniaturized for use as an implant to administer an agent to an animal. It is shown in an open view along line 8-8 and comprises a wall 41 that retains its shape, formed at least partly from a semipermeable material that surrounds an internal swellable pouch element 42. This pouch 42 is an open vessel with an internal space 43 and an opening 50 well closed by a closure piece 44 traversed by inlet and output openings for supply and delivery. Pouch 42 contains an agent and a composition of heat-sensitive vehicle 47 for this agent. A passage 49 in a semipermeable wall 41 is aligned with opening 45 to fill the device 10 and to cause agent 46 to emerge.

Figures 1 to 9 show different devices according to the present invention but do not limit it in any way and can have a variety of shapes and dimensions to deliver agents to the surrounding use medium. For example, the device can be designed for oral administration in different shapes and common sizes, for example, with dimensions of 5 to 25 mm or for use as an implant, artificial gland, cervical, intrauterine, auricular, nasal, dermal, vaginal, rectal device, in the belly or second stomach of ruminants or a subcutaneous device. It can also be in a shape and with dimensions and structures adapted to deliver an agent into rivers, aquariums, fields, factories, reservoirs, laboratories, greenhouses, vehicles, hospitals, shipyards, for military purposes, veterinary clinics, rest homes, farms, zoos, chemical reactors, etc.

DETAILED DESCRIPTION OF THE INVENTION

It has surprisingly been found that the delivery device 10 can be provided with a wall containing a semipermeable material without harm to the recipient, permeable to passage to an external aqueous liquid, like water or biological fluid, or remaining virtually impermeable to passage of agents, like drugs, osmotic agents and which maintains its integrity in the presence of a thermotropic composition. The selectively semipermeable materials forming the external wall are virtually insoluble in liquids and are not toxic and not erodable.

Representative materials to form the semipermeable wall include semipermeable homopolymers and copolymers, etc., and in one version the characteristic materials include cellulose esters, monoesters, diesters and triesters, cellulose ethers and cellulose esters-ethers. These cellulose polymers have a degree of substitution (DS) on their anhydroglucose unit greater than zero and it can amount to as much as 3, the degree of substitution being understood to mean the average number of hydroxyl groups initially present on the anhydroglucose unit and which are replaced by a substituent and converted to other groups. The anhydroglucose unit can be fully or partially substituted with groups like acyl, alkanoyl, aroyl, alkyl, alkenyl, alkoxy, groups, halogens, carboalkyl groups, alkyl carbamates, alkyl carbonates, alkyl sulfonates, alkyl sulfamates and other similar groups forming a semipermeable polymer.

The semipermeable materials characteristically include the following: cellulose acylate, diacylate and triacylate, like cellulose acetate, diacetate and triacetate, cellulose mono-, di- and trialkylates, mono-, di- and trialkenylates and mono-, di- and triaroylates etc. Examples of polymers include cellulose acetate with an DS from 1.8 to 2.3 and an acetyl content from 32 to 39.9%; cellulose diacetate having a DS from 1 to 2 and an acetyl content from 21 to 35%; cellulose triacetate having a DS from 2 to 3 and an acetyl content of 34 to 44.8%, etc. Cellulose polymers, in particular, include cellulose propionate having a DS of 1.8 and a propionyl content of 38.5%; cellulose acetate-propionate having an acetyl content of 1.5 to 7% and a propionyl content from 39 to 42%; cellulose acetate-propionate having an acetyl content of 2.5 to 3%; an average propionyl content of 39.2 to 45% and a hydroxyl content of 2.8 to 5.4%; cellulose acetate-butyrate having a DS of 1.8, an acetyl content of 13 to 15% and a butyryl content of 34 to 39%; cellulose acetate-butyrate having an acetyl content of 2 to 29.5%, a butyryl content of 17 to 53% and a hydroxyl content of 0.5 to 4.7%; cellulose triacylates having a DS of 2.9 to 3, like cellulose trivalerate, trilaurate, tripalmitate, trioctanoate and tripropionate; cellulose diesters having a DS of 2.2 to 2.6, like cellulose disuccinate, dipalmitate, dioctanoate, dicaprylate and others; mixed esters of cellulose, like cellulose acetate-valerate, acetate-succinate, propionate-succinate, acetate-octanoate, valerate-palmitate and acetate-heptanoate, etc. Semipermeable polymers are known from US Patent 4 077 407 and can be obtained by the methods described in the Encyclopedia of Polymer Science and Technology, volume 3, pages 325 to 354, 1964, published by Interscience Publishers, Inc., New York.

Other semipermeable polymers include cellulose acetaldehyde-dimethyl acetate, cellulose acetate-ethyl carbamate, cellulose acetate-methyl carbamate, cellulose dimethylaminoacetate, semipermeable polyamides, polyurethanes and polysulfanes [sic], semipermeable crosslinked sulfonated polystyrenes, selectively semipermeable polymers formed by coprecipitation of a polyanion and a polycation, as described in US Patents 3 173 876,

3 276 586, 3 541 005, 3 541 006 and 3 546 142, selectively semipermeable silicone rubbers, semipermeable polymers, as described by Loeb and Sourirajan in US Patent 3 133 132, semipermeable polystyrene derivatives (sodium polystyrene sulfonate, semipermeable poly(vinylbenzyltrimethyl)ammonium chloride, semipermeable polymers having a liquid permeability of 10^{-1} to 10^{-7} cm^3·mil (25.4 μm) per cm^2 per hour, per atm, expressed per atm hydrostatic or osmotic pressure difference through the semipermeable wall. These polymers are known from US Patents 3 845 770, 3 916 899 and 4 160 020 and are also found in the Handbook of Common Polymers by Scott, J. R. and Roff, W. J., 1971, published by CRC Press, Cleveland, Ohio.

The materials used to form the internal swellable wall that dilates and the pouch are polymer materials, alone or mixed with osmotic agents that react with water or a biological fluid, absorbing the liquid and swelling by dilating to a state of equilibrium. The polymer has the capacity to retain a substantial fraction of liquid impregnating it and the preferred polymers are polymer gels that can swell and dilate to a very high degree, generally from 2 to 50 times their volume. Hydrophilic polymers that swell, also called osmopolymers, can be uncrosslinked or slightly crosslinked. The transverse bonds can be covalent or ionic bonds for a polymer that can swell in the presence of a liquid and, if it is crosslinked, it does not dissolve in the liquid. The polymer can be of plant, animal or synthetic origin. Interesting polymer materials here include a hydroxyalkyl polymethacrylate with a molecular weight from 5000 to 5,000,000; a polyvinylpyrrolidone with a molecular weight from 10,000 to 360,000; anionic or cationic hydrogels, polyelectrolyte complexes; polyvinyl alcohol with a low residual acetate content; a swellable mixture of agar and carboxymethylcellulose; a swellable composition containing methylcellulose mixed with slightly crosslinked agar; a polymer that swells in water formed by dispersion of a finely divided copolymer of maleic anhydride with styrene, ethylene, propylene or isobutylene; polymers that swell in water from N-vinyllactams, etc.

Other gelifiable polymers that retain the impregnation liquid and are of interest to form the dilatable hydrophilic thrust element include pectin having a molecular weight from 30,000 to 300,000; gelatin having a viscosity from 15 to 30 millipoises and a strength that can reach 150 g, gelatin having a Bloom value of 160 to 250; polysaccharides, like agar, gum arabic, karaya gum or gum tragacanth, algins and guar gum; an acid carboxy polymer Carbopol® and its salt derivatives; polyacrylamides, polymers of indene and maleic anhydride that swell in water; Good-rite® polyacrylic acid having a molecular weight of 80,000 to 200,000; Polyox® polyoxyethylene polymers having a molecular weight of 100,000 to 5,000,000; graft copolymers of starch; Aqua-Keep® polyacrylates that absorb about 400 times their initial weight in water; diesters of polyglucan; a mixture of crosslinked polyvinyl alcohol and polyvinylpyrrolidone; zeins in the form of prolamine; polyethylene glycol having a molecular weight of 4000 to 100,000, etc. In a preferred variant, a dilatable wall is formed with polymers and polymer compositions that can be shaped while hot. Representative polymers having hydrophilic characteristics are known from US Patents 3 865 108, 4 002 173, 4 207 893 and 4 327 725 and are also found in the Handbook of Common Polymers by Scott and Ruff, published by Cleveland Rubber Company, Cleveland, Ohio.

The compounds of osmotic action that can be mixed homogeneously or heterogeneously with the swellable polymer to form a thrust wall are solutes with osmotic action that are soluble in the liquid impregnating swellable polymer and exert an osmotic pressure gradient through the semipermeable wall against an external liquid. The compounds with osmotic action are also called osmogents. Effective osmogents for the proposed objective include magnesium sulfate and chloride, sodium chloride and lithium chloride, potassium sulfate and sodium sulfate, mannitrol, urea, sorbitol, inositol, sucrose, glucose and others. The osmotic pressure in atmospheres (atm) of appropriate osmogents here is greater than 0 atm, and generally between 8 atm and 500 atm or more.

The swellable, expandable polymer ensures not only the thrust force to deliver the medical agent from the delivery device, but also serves as support matrix for an osmotically suitable solute. The osmotic solute can be mixed homogeneously or heterogeneously with the polymer so that the desired swellable wall or swellable pouch is formed. The composition contains in the now preferred variant at least one polymer and at least one osmotic solute. Generally, a composition contains about 20 to 90 wt% polymer and 80 to 10 wt% osmotic solute with a preferred composition of 35 to 75 wt% polymer and 65 to 25 wt% solute.

The term agents denote any composition or formula or any compound that can be delivered to produce an interesting specified result. The agents include algicides, antioxidants, air purifiers, biocides, catalysts, chemical reagents, cosmetics, drugs, disinfectants, fungicides, foods, fertility inhibitors or fertility activators, food supplements, fermentation agents, germicides, insecticides, attenuators of microorganisms, nutrients, products for plant growth and growth inhibitors, preservatives, surfactants, sterilizants, sexual sterilizants, vitamins and other beneficial products for the environment and surroundings, habitats and animals. These agents can be insoluble or highly soluble in the temperature-sensitive material that is placed in the delivery device.

The term drug in the description and claims is understood to mean any substance having a physiological or pharmacological action that produces a local or systemic effect in animals, including warm-blooded mammals, man

and primates, birds, fish and domestic animals, game animals and farm animals, laboratory animals and zoo animals. The term physiological denotes administration of the drug to produce normal levels and functions and the term pharmacological denotes variations in response to amounts of the drug that are administered to the host.(see Stedman's Medical Dictionary, 1966, published by Williams and Wilkins, Baltimore, MD). The drugs that can be administered include mineral or organic drugs without limits, drugs that act on the nervous system, depressants, hypnotics, sedatives, psychological stimulants, tranquilizers, anticonvulsants, muscle relaxants, antiparkinsonian agents, analgesics, antiinflammatories, antimalarials, hormonal agents, contraceptives, sympathicomimetics, diuretics, antiparasitics, neoplastic drugs, hypoglycemic drugs, ophthalmic drugs, electrolytes, diagnostic products and cardiovascular drugs. The amount of agent that the delivery device contains can be from 0.05 ng to 20 g or more. For medical applications the device can contain various amounts, for example, 25 ng, 1 mg, 5 mg, 125 mg, 250 mg, 500 mg, 750 mg, 1.5 g, etc. and the device can be used once, twice or three times a day, twice a week or differently.

Compositions that respond to the effect of heat are referred to as heat-sensitive compositions and are thermoplastic compositions that can soften or be delivered to the medium under the influence of heat and reharden when cooled and this also includes thermotropic compositions that can undergo modifications in response to application of an energy gradient. These compositions are sensitive to an increase or reduction in temperature. The expression heat-sensitive denotes a physicochemical property of a composition of agent and vehicle that makes it solid or semiliquid at temperatures up to 34°C, generally between 20 and 33°C and becoming liquid, semisolid or viscous under the influence of heat from 33°C, generally between 33 and 40°C. The heat-sensitive vehicle melts, is totally or partially dissolved, softens or liquefies at elevated temperatures, which enables it to be delivered to the considered medium with the agent that it contains in a homogenous or heterogeneous mixture. The heat-sensitive vehicle can be lipophilic, hydrophilic or hydrophobic and another important characteristic of the vehicle is that it can maintain the stability of the agent that it contains during storage and delivery of the agent. Representative heat-sensitive compositions given with their melting point are as follows: cocoa butter 32-34°C; cocoa butter with 2% beeswax 35-37°C; propylene glycol monostearate and distearate 32-35°C; hydrogenated oils, like vegetable oils 36-37°C; 80% of a hydrogenated vegetable oil with 20% sorbitan monopalmitate 39-39.5°C; 80% of a hydrogenated vegetable oil with 20% polysorbate 60, 36-37°C; 77.5% of a hydrogenated vegetable oil with 20% sorbitan trioleate and 2.5% beeswax, 35-36°C; 72.5% of a hydrogenated vegetable oil, 20% sorbitan trioleate, 2.5% beeswax and 5% distilled water, 37-38°C; mono-, di- and triglycerides of C_8 to C_{22} acids containing saturated and unsaturated acids, like palmitic, stearic, oleic, linoleic, linolenic and arachidonic acids; saturated fatty acid triglycerides with mono- and diglycerides, 34-35.5°C; propylene glycol mono- and distearates, 33-34°C; partially hydrogenated cottonseed oil, 35-39°C; hydrogenated and aliphatic alcohols 33-36°C; hexadienol and anhydrous lanolin triethanolamine glyceryl monostearate 38°C; eutectic mixtures of mono-, di- and triglycerides, 35-39°C; Witepsol® 15, saturated fatty acid triglycerides of plant origin with monoglycerides, 33.5-35.5°C; Witepsol® H32 without hydroxyl, 31-33°C; Witepsol® W25 having a saponification index of 225-240 and a melting point of 33.5-35.5°C; Witepsol® E75 with a saponification index of 220-230 and a melting point of 37-39°C; a polyalkylene glycol, like polyethylene glycol 1000, a linear polymer of ethylene oxide 38-41°C; polyethylene glycol 1500, 38-41°C; monoethylene-polyethylene glycol, 39-42.5°C; 33% polyethylene glycol 1500, 47% polyethylene glycol 6000 and 20% distilled water, 39-41°C; 30% polyethylene glycol 1500, 40% polyethylene glycol 4000 and 30% polyethylene glycol 400, 33-38°C; a mixture of mono-, di- and triglycerides of saturated fatty acids with 11 to 17 carbon atoms, 33-37°C, etc. The heat-sensitive composition is a means to conserve an agent in the solid composition at temperatures from 20 to 33°C, maintaining a nonmiscible separation limit at the interface of the composition that swells, and delivering the agent in a fluid composition at a temperature generally greater than 33°C, ordinarily from 33 to 40°C. The heat-sensitive composition that is delivered to the surrounding biological medium can be easily excreted, metabolized, assimilated, etc. for effective use of the agent.

The semipermeable wall can be applied to the heat-sensitive dilatable layer stratified by molding, shaping, spraying or immersion in a material forming this wall.

Other techniques that are now preferable and permit application of the semipermeable wall include suspension in air and pan coating processes. The air suspension method consists of suspending the stratified layer or pouch in a stream of air and allowing it to roll with a composition forming the semipermeable wall until the wall surrounds and encloses it, and this operation is repeated with a composition forming a different semipermeable wall to obtain a semipermeable stratified wall. The air suspension process is described in US Patent 2 799 241 and in J. Am. Pharm. Assoc., volume 48, pages 451 to 459, 1979, and ibid, volume 49, pages 82 to 84, 1960. Other methods for production are described in Modern Plastics Encyclopedia, volume 46, pages 62 to 70, 1969 and Pharmaceutical Sciences by Remington, 14th edition, pages 1626 and 1678, 1970, publication of Mack Publishing Co., Easton, PA.

Solvents that suitable for production of the semipermeable wall include mineral or organic solvents without drawbacks for the employed materials, dilatable wall, pouch, heat-sensitive composition and final delivery device. These solvents include generally aqueous solvents, alcohols, ketones, esters, ethers, aliphatic hydrocarbons, halogenated solvents, cycloaliphatic solvents, aromatic or heterocyclic solvents and their mixtures, the characteristic solvents being acetone, diacetone alcohol, methanol, ethanol, isopropyl alcohol, butyl alcohol, methyl, ethyl, isopropyl, n-butyl acetates, methyl isobutyl ketone, methyl propyl ketone, n-hexane, n-heptane, ethylene glycol monoethyl ether, ethylene glycol monoethyl acetate, methylene, ethylene or propylene dichloride, carbon tetrachloride, nitroethane, nitropropane, tetrachloroethane, ethyl ether, isopropyl ether, cyclohexane, cycloheptane, benzene, toluene, solvent naphtha, 1,4-dioxane, tetrahydrofuran, diglyme, water and their mixtures, like a mixture of acetone and water, acetone and methanol, acetone and ethyl alcohol, methylene dichloride and methanol or ethylene dichloride and methanol. Ordinarily the semipermeable wall is applied at a temperature lower by a few degrees than the melting point of the heat-sensitive composition or the thermoplastic composition can be placed in the delivery device after having applied the semipermeable wall.

The dilatable wall, the pouch or dilatable layer can be made by known polymerization processes of heat shaping, for example spraying on a mandrel, immersion of the mold in the composition forming the wall, molding by blowing, formation under vacuum, molding by compression or injection, extrusion and stratification. But in a now preferred variant, a pouch or thrust compartment is molded by the compression process illustrated in Figure 10. In this compression process, a mold cavity and a piston are used. The mold cavity forms one surface of the molded part and the composition forming the polymer wall is placed in the mold, the piston of the mold forming the other surface of the pouch. The piston compresses the composition and, when the mold is closed, the composition is compressed to the shape of the final pouch, the mold cavity and piston being kept in this position until the composition has hardened. In Figure 10 the molded pouch or thrust compartment is denoted with the letter a and is seen when withdrawn from the compression mold. The pouch is then placed in a filling position beneath a filling hopper and filled with a formula of the molten agent. After cooling, the filled compartment is covered at c with a semipermeable wall in which a delivery opening is perforated with a laser. In a similar process, the molded compartment is closed (at d) with a closure containing a filling opening and a discharge opening and it is filled at the filling station e at ordinary temperature with a formula of the molten agent. Finally the filled compartment is covered at f with a semipermeable wall traversed by a laser-perforated opening in axial arrangement with the opening, which produces the delivery device. In a similar process the closed compartment is covered with a membrane or semipermeable wall traversed by a laser-perforated opening in the axial position relative to the opening, which produces the empty device denoted with letter g, which is then filled at ordinary temperature with the formula of the molten agent, which produces the final device h.

The passage opening through the semipermeable wall permits release of the formula of the agent of the delivery device. The opening can be formed mechanically or by a laser or by erosion of an erodable element of the wall, for example, a gelatin plug. A detailed description of openings and their maximum and minimum preferable dimensions is given in US Patents 3 845 770 and 3 916 899.

DESCRIPTION OF THE EXAMPLES

The following examples are given only as illustrations and in no way limit the application possibilities of the invention.

Example 1

A delivery device is formed as follows: by molding by injection a polymer composition a dilatable vessel is first formed in the shape of a capsule 12 mm in diameter and 40 mm deep whose wall is formed from a composition containing 30 wt% sodium chloride and 70% polyoxyethylene with a molecular weight of 3,000,000, which are mixed for 20 minutes to produce a homogeneous composition. This composition is pressed into tablets that are placed in an injection molding machine and the vessel formed by injection molding at 145-150°C under a pressure of 6.5-7.0 × 10 kPa.

This vessel is then provided with a heat-sensitive composition containing 0.5 wt% theophylline, 77% of a hydrogenated vegetable oil, 20% sorbitan trioleate and 2.5% beeswax at a temperature of 36-37°C and, after cooling at 20°C, the vessel equipped with an external semipermeable wall is coated in a Wurster air suspension coater. The semipermeable wall is formed from a solution in methylene chloride of 5 wt% cellulose acetate-butyrate and it is applied to a thickness of 0.4 mm. The devices so equipped are dried in a drying cabinet at 50°C for 5 to 10 days and

an opening of 0.75 mm is then perforated with a laser through the semipermeable wall, permitting delivery of the drug formula from the compartment to the external medium.

Example 2

The vessel or pouch with a large opening is prepared as in example 1, which is provided with a drug formula containing 0.20 g paracetamol, 0.02 g codeine phosphate, 0.15 g acetyl salicylic acid and 2.0 g Witepsol® H35, a mixture of esters of glycerol and saturated fatty acids of plant origin in which lauric acid predominates. This composition is prepared by triturating and mixing all the drug substances and then adding the vehicle Witepsol at 38-40°C, the pouches are filled with the molten composition, which after cooling has a creamy consistency and the pouch then covered with a semipermeable wall in which an opening is made with a laser in the manner previously mentioned.

Example 3

A delivery device containing a compartment with a heat-sensitive composition in a stratified arrangement is formed as follows with a dilatable composition: a molten composition of 2.5% phenobarbital, 20.5% glycerogelatin and 77.0% theobroma oil, stearic, palmitic and lauric acid glycerides are placed successively in a mold to form the heat-sensitive layer after cooling to ordinary temperature, whereupon a mixture of 30 parts ethylene glycol monomethacrylate and 0.12 parts ethylene glycol dimethacrylate and 10 parts of an aqueous solution of 0.13% sodium bisulfate in aqueous ethanol is placed in the mold. This mixture is polymerized at 30°C and 20 minutes after equilibrium at ordinary temperature the solid layer is removed from the mold.

A solution in acetone of 15 wt% cellulose acetate is then prepared having an acetyl content of 39.8%, with which the stratified layer is covered by immersing it 15 times in the solution, once for 10 seconds, then the other times for 1 minute with intermediate drying of 5 minutes, and after these immersions the devices are dried at ordinary temperature at 22°C for 10 days. A semipermeable wall of 0.7 mm is thus applied, which controls the flow rate of the wall through which a passage is made with a laser to connect the exterior of the device to the heat-sensitive layer.

Example 4

A delivery device is formed as follows: a heat-sensitive eutectic mixture to be liquefied consisting of 77% of a neutral fat that melts at 35-37°C and 19.5% of paraffin wax melting at 52°C are heated, 3.5% acetylsalicylic acid is added to the liquid and the mixture placed in a mold. After cooling and solidification, 500 mg of polyacrylamide Cyanamer®, a hydrogel having a molecular weight of about 200,000 is added, the layers are pressed to form a heat-sensitive layer in contact with the hydrogel layer and the layers in contact are removed from the mold.

A semipermeable wall is then formed by mixing 85 g cellulose acetate with 39.8% acetyl groups with 200 mL methylene chloride and 200 mL methanol and covered by spraying the compartment with two layers in an air suspension machine until a 0.25 mm semipermeable wall encloses the compartment. The devices are dried for 2 weeks and then a 0.4 mm passage is made in the semipermeable wall with a laser, which communicates with the heat-sensitive composition.

Example 5

The process of example 4 is repeated with the indicated compositions, except that the heat-sensitive composition contains a polyethylene ether of a partial fatty acid ester and an internal polyhydroxyl cyclic ether containing the drug, the polyoxyethylene ether having from 2 to 4 ethylene oxide groups and the partial fatty acid ester having from 14 to 18 carbon atoms. The composition contains a drug and the heat-sensitive composition melts rapidly and completely at body temperature, liquefying for easy delivery from the device to the external medium.

Example 6

The processes of examples 4 and 5 are repeated to form a heat-sensitive composition containing 85 mg sorbitan monostearate epoxidized with 4 units with a melting point of 38°C, 5 mg sorbitan monostearate epoxidized with 20 units, 5 mg sorbitan monoricinoleate and 15 mg sodium indomethacin.

Example 7

The heat-sensitive composition is prepared for the device of example 1 by mixing while hot 30% polyethylene glycol 1500 with 30% polyethylene glycol 4000, 30% polyethylene glycol 400, 9% cocoa butter and 1% oxyprenolol hydrochloride, a composition that melts in 15 to 20 minutes at a temperature of 37°C.

Example 8

An osmotic capsule is injection molded in the form of a cylinder with thin walls and hemispherical bottom with a composition containing 65% sodium chloride, 20% of the product Polyox®, an ethylene oxide polymer having a molecular weight of about 200,000, and 15% polyethylene glycol 200,000, the injection conditions under which the capsule is molded being as follows:

Nozzle temperature	180±20°C
Zone 1	off
Zone 2	230±25°C
Zone 3	220±25°C
Temperature of hot point	180±25°C
Temperature of mold cavity	18±3°C
Temperature of central passage	8±3°C
Temperature of blocking plate	8±3°C
Illumination time	13.5±2 sec
Injection time	1.9±0.5 sec
Injection rate	5±1
Injection pressure	84±7 bars
Recoil pressure	42±7 bars
Cycle time	20 sec

The inside and outside diameters and inside and outside lengths are 1.17 cm and 1.33 cm and 3.70 cm and 3.85 cm respectively.

This osmotic capsule is provided with 2.88 g of Witepsol® H15, a glycerol ester of a saturated fatty acid of plant origin with 0.1% red dye oil and it is covered with cellulose acetate-butyrate in a pan coater (Accela-Cota) in a solvent of 95% dichloromethane and 5% ethanol) to regular formation of a semipermeable membrane 0.5 mm thick. The capsules are dried at 55°C for 7 days, whereupon an outlet opening 1 mm in diameter is perforated and the release rate examined. The appended drawings of Figure 11 show the release rate of the heat-sensitive composition in mg/h for a day and Figure 12 shows the cumulative amount of heat-sensitive composition liberated in percent of the total amount liberated from the system. The circles indicate liberation of the system in the vertical position and the squares indicate liberation of the system in the horizontal position.

One variant of this invention concerns a method for administering a drug at a controlled flow rate by the vaginal or anorectal route to a warm-blooded animal, a method according to which: (A) a delivery device is introduced to the passage containing: (1) an internal wall formed from a polymer composition that dilates by swelling, surrounding and delimiting an internal compartment; (2) an opening in this internal wall; (3) a drug formula in the compartment containing a number of dose units of the drug for a therapeutic program with a heat-sensitive vehicle that melts or dissolves at body temperature and serves to cause the drug to emerge from the delivery device; (4) an external wall enclosing the pouch and opening, a wall formed from a semipermeable polymer composition, permeable to liquids but impermeable to drugs; and (5) an opening in this external wall that communicates through the opening with the internal compartment; (B) the body fluid impregnates the internal wall through the semipermeable wall at a rate determined by the permeability of this wall and the osmotic pressure gradient through this semipermeable wall, which causes the internal wall to swell and dilate; (C) the drug formula melts in the compartment, forming a fluid composition; and (D) release of the drug formula from the compartment through the internal wall that swells and dilates relative to the molten formula which passes the formula in the desired therapeutic amount through the opening at a controlled flow rate to the passage route to produce the desired medical effect over an extended period from one or more months, preferably from 1 hour to 24 hours.

To the extent that the preceding description contains preferred variants of the invention, it is noted that variations and adaptations according to the disclosed inventive principles can be employed without departing from the cope of the invention.

Claims

1. A device for delivery to a surrounding medium at a controlled flow rate of a formula of a medical agent sensitive to the effect of heat characterized by:

a) an internal wall surrounding and forming an internal compartment to contain the formula of the agent with an opening in this wall to fill it with the formula and cause it to emerge, this wall being formed by a composition to absorb the liquids by swelling and by dilating in the compartment;

b) an external wall surrounding the internal wall, an external wall that is formed from a composition permeable to passage of liquids but almost impermeable to passage of an agent; and

c) a passage in the external wall that communicates with the opening to deliver the preparation of a medical agent to the surrounding medium.

2. Delivery device according to Claim 1, characterized by the fact that the compartment contains a formula of an agent that remains solid to 33°C and melts above this temperature.

3. Delivery device according to Claim 1 or 2, characterized by the fact that the internal wall is formed from a composition containing a polymer hydrogel and a solute with osmotic action.

4. Delivery device according to Claim 1 or 2, characterized by the fact that the internal wall is formed from a composition containing a polymer hydrogel that swells and dilates in the presence of a liquid.

5. Delivery device according to Claim 1-4, characterized by the fact that a closure element is contained in the opening of the wall with a perforation in the closure element.

6. Delivery device according to Claim 1-5, characterized by the fact that the external wall is formed from a material chosen from the following: esters, diesters, ethers, esters and ethers of cellulose, cellulose acylates, diacylates, triacylates, cellulose acetate, diacetate, triacetate and acetate-butyrate.

7. Delivery device according to Claim 1-5, characterized by the fact that the external wall is formed from the hydrophilic composition that swells and in the presence of aqueous impregnation liquids.

8. Delivery device according to Claim 1 or 2, characterized by the fact that the internal wall is formed from polyethylene oxide.

9. Delivery device according to Claim 1 or 2, characterized by the fact that the internal wall is formed from polyethylene oxide, polyethylene glycol and a solute with osmotic action.

10. Delivery device according to Claim 1-9, characterized by the fact that the compartment contains a heat-sensitive composition containing an ester of glycerol and saturated fatty acids.

11. Delivery device of a medical agent at a controlled flow rate to a surrounding medium of biological fluid at a temperature greater than 33°C, characterized by:

a) a wall formed from a semipermeable polymer composition that surrounds and defines:

b) a compartment;

c) a first means in the compartment to convert a solid composition to a composition deliverable under the influence of the temperature of the biological medium, this first means containing an agent and being in contact with the second means in the compartment to be impregnated with liquid through the semipermeable wall and to dilate in the compartment; and

d) a passage in the wall that connects the exterior device to the first means.

12. Delivery device according to Claim 11, characterized by the fact that the first means is a layer.

13. Delivery device according to Claim 11 or 12, characterized by the fact that the second means is a layer.

14. Delivery device according to Claim 11-13, characterized by the fact that the solid composition is a gel.

15. Delivery device according to Claim 11-14, characterized by the fact that the solid composition melts at the temperature of the surrounding biological medium.

16. Delivery device according to Claim 11-14, characterized by the fact that the solid composition liquefies at the temperature of the surrounding biological medium.

17. Delivery device of a medical agent at a controlled flow rate to a surrounding liquid medium whose temperature is that of a warm-blooded animal, characterized by:

a) a wall formed from a semipermeable polymer composition that defines a tube closed with an internal space;

b) a first means placed in the center of this space to convert a nondeliverable composition to a deliverable composition at the temperature of the surrounding medium, a means containing an agent and surrounded by a second means in the space that is impregnated with liquid through the semipermeable wall and dilates against the first means; and

c) a passage in the wall communicating with the exterior device and the first means.

18. Delivery device according to Claim 17, characterized by the fact that the second means is placed between the first means and the internal surface of the wall.

19. Delivery device according to Claim 17 or 18, characterized by the fact that the passage in the wall is found on the closed end of the tube.

20. Delivery device according to Claim 17-19, characterized by the fact that the composition that cannot be delivered is a semisolid composition.

21. Delivery device according to Claim 17-19, characterized by that fact that the composition that cannot be delivered is a solid composition.

22. Delivery device according to Claim 17-19, characterized by that fact that the composition that cannot be delivered does not flow at a temperature lower than 33°C.

23. Delivery device of a medical agent, characterized by:

a) a body of tubular shape closed on its ends, which is formed from a polymer composition permeable to passage of an external liquid but practically impermeable to passage of the agent;

b) a compartment in the body;

c) a first layer in the compartment formed by a composition containing an agent and a vehicle for this agent;

d) a second layer in the compartment in contact with the first layer, formed from a hydrogel that dilates in the presence of a liquid penetrating into the compartment; and

e) a passage in the body that connects the exterior device to the first layer.

24. Delivery device according to Claim 23, characterized by the fact that the vehicle is a nontoxic hydrogenated oil for pharmaceutical use.

25. Delivery device according to Claim 23, characterized by that fact that the vehicle is chosen from nontoxic monoglycerides, diglycerides and triglycerides.

26. Delivery device according to Claim 23, characterized by the fact that the vehicle is a hydrophilic, nontoxic material having a molecular greater than 1000.

27. Delivery device according to Claim 23, characterized by the fact that the vehicle is a eutectic nontoxic composition containing a glyceride and a hydrogenated oil.

28. Delivery device according to Claim 23, characterized by the fact that the vehicle is a nontoxic glyceride of a fatty acid having 8 to 12 carbons atoms.

29. Delivery device according to Claim 23, characterized by the fact that the vehicle is a nontoxic composition containing a mixture of at least two polyethylene glycols, one of which has a molecular weight greater than 1000.

30. Delivery device at a controlled flow rate of a formula of medical agent sensitive to heat to the surrounding use medium, characterized by:

a) an internal wall surrounding and forming an internal compartment that contains the formula of the agent with an opening in the wall to fill the compartment with the formula of the agent and to cause it to emerge, a wall that is formed from a composition that absorbs the liquid by swelling and dilating around the compartment;

b) an external wall surrounding the internal wall, an external wall that is formed from a composition permeable to the passage of a liquid but practically impermeable for passage of the agent, a composition comprising material chosen from polysulfone, polyacrylate, polymethacrylate, polymethylmethacrylate and polyurethane; and

c) a passage in the external wall that communicates with the delivery opening of the device for the preparation with a medical agent.

Figure 10.
(a) Thrust compartment molded
(b) Filling of the compartment with the molten formulation of active agent
(c) Enclosing of the semipermeable wall and perforation of the opening
(d) Compartment sealed with its closure
(e) Filling
(f) Enclosure of the semipermeable wall and perforation of the opening
(g) Enclosure of the semipermeable wall and perforation of the opening
(h) Filling

Figure 11.
Osmotic delivery pump of Witepsol H-15
Mean ± Standard deviation
• Vertical position

■ Horizontal position
Delivery rate of Witepsol, mg/h
Residence time, days

Figure 12.
Witepsol total delivery in %
Residence time, days